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(54) Title: THE PROCESS OF MANUFACTURING PHARMACEUTICAL GRADE TANNATES

(57) Abstract: Antihistamines are available in the form of free bases as well as salts i.e. hydrochloride, maleate, tannate, etc. Frequently, it is necessary to utilise antihistamines in the form of tannate salt because such salts are generally quite stable and may be administered in such from without untoward side effects. Tannic acid, also known as tannin, is a well known naturally occurring substance. Tannic acid, which is available commercially, usually contain about 5 % of water, has a molecular weight of about 1700 and is typically produced from Turkish or Chinese nutgall. Antihistamine tannates, presently manufactured commercially, are relatively impure. Such tannates are prepared by the reaction of antihistamine free base with tannic acid and using a volatile solvent, isopropanol (IPA). The yield is only fair (around 70 %) and decomposition products e.g. 2-5 % along with significant amount of volatile solvent, isopropanol (6-10 %) remains with the product, which cannot be removed. According to present invention, isopropanol is removed by using a solvent for isopropanol which I highly volatile, which does not dissolve tannates but disperses the wet cake of tannate. The solvent, hexane, is added to wet cake while stirring it and the it is filtered. This results in residue of tannates with lower isopropanol content. The drying results into pharmaceutical grade tannate.

1. THE PROCESS OF MANUFACTURING PHARMACEUTICAL GRADE TANNATES

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3. The following specification particularly describes and ascertains the nature of this invention and the manner in which it has to be performed.

FIELD OF THE INVENTION

The objective of the present invention is to manufacture pharmaceutical grade tannates.

The further objective of the present invention is to manufacture pharmaceutical grade tannates using hexane as a solvent for removing isopropanol, thereby reducing the content of isopropanol.

The further objective of present invention is to improve the yield of pharmaceutical grade tannates.

BACKGROUND OF THE INVENTION

Antihistamines are available in the form of free bases as well as salts i.e hydrochloride, maleate, tannate etc. Frequently, it is necessary to utilise antihistamines in the form of tannate salt because such salts are generally quite stable and may be administered in such from without untoward side effects. Tannic acid, also known as tannin, is a well known naturally occurring substance. Tannic acid, which is available commercially, usually contain about 5% of water, has a molecular weight of about 1700 and is typically produced from Turkish or Chinese nutgall.

Antihistamine tannates, presently manufactured commercially, are relatively impure. Such tannates are prepared by the reaction of antihistamine free base with tannic acid and using a volatile solvent, isopropanol (IPA). The yield is only fair (around 70%) and decomposition products e.g. 2-5% along with significant amount of volatile solvent, isopropanol (6-10%) remains with the product, which cannot be removed. As per guidelines for pharmaceutical agents, the residual solvents should be less than 0.5% or 5000 ppm.

Many antihistamine tannates are heat sensitive e.g. phenyleherine tannates and therefore undergo decomposition quite readily upon prolonged exposures to temperatures as low as 50°C. Accordingly, even if the solvent utilized in its preparation has relatively high vapour pressure e.g. as in isopropanol, it is impossible to reduce the solvent content below 6% based on the weight of antihistamine tannate even at reduced pressures and very mild elevated temperatures. Morever from environment point of view, it would be desirable if antihistamine tannates would be manufactured such that use of volatile solvents like isopropanol would be avoided.

US patent 5663415 describes a method by treating the antihistamine tannate in isopropanol with tannic acid in isopropanol at 60-80°C for 1-2 hours. The resulting antihistamine tannate has isopropanol 8-10% and cannot be removed on prolonged heating under vacumn.

Similarly, in US patent 5599846, phenyleherine tannate was synthesized by isopropanol route. The resulting antihistamine tannate had isopropanol 8% and 2% degradation products.

REFERENCES:

1. U.S. Patent No. 5663415:
Process for preparing antihistamine tannates.
Chopdekar VM et al.
Jame Fine Chemicals, Inc.

2. US Patent no. 5599846.
Phenylehedrine tannates composition.
Chopdekar VM et al.
Jame Fine Chemicals, Inc.

SUMMARY OF THE INVENTION

It has now been found that it is possible to reduce the content of isopropanol to around 3% during the manufacture of pharmaceutical grade tannates. This is possible by using hexane as a solvent.

According to the present invention, the content of isopropanol has been found to be around 3%.

DESCRIPTION OF THE INVENTION

According to the present invention is described a method to manufacture pharmaceutical grade tannates, using hexane as a solvent.

Isopropanol is charged. Tannate base is added to this isopropanol. Tannic acid solution is prepared by dissolving in isopropanol. The above Tannic acid prepared is added into Tannate base solution. The solution is stirred for 3 hours at 40-50°C. This is then cooled to 20-25°C. The material is centrifuged and washed with a solvent, hexane. The material is then unloaded. The product is dried.

EXAMPLE 1- PHENYLEPHRINE TANNATE:

Isopropanol :	1200 ml
Phenylephrine base:	20 gms
Tannic acid:	39.4 gms in 400 ml isopropanol
Hexane:	1000 ml

1200 ml of isopropanol is charged to which 20 gms base is added. Tannic acid is prepared by dissolving 39.4 gms in 400 ml isopropanol, which is then added to base solution. The solution is stirred for 3 hours, cooled and filtered. This then washed with hexane and dried.

The above tannate prepared reveals the following, with a yield of 30 gms :

1. Description: pale yellow, tan fine powder
2. Water: 3.32% w/w
3. Residue on ignition: 0.15%
4. Heavy metals: Less than 5 ppm
5. Tannic acid: 62.93% w/w
6. Phenylephrine base: 34.39% w/w
7. Assay: 99.50% w/w
8. Residual solvents: Isopropanol: 6088 ppm

EXAMPLE 2- CHLORPHENIRAMINE TANNATE

Isopropanol:	850 ml
Chlorpheniramine base:	43.3 gms
Tannic acid:	40.7 gms in 450ml Isopropanol
Hexane:	1000 ml

850 ml of isopropanol is charged to which 43.3 gms base is added. Tannic acid is prepared by dissolving 40.7 gms in 450 ml isopropanol, which is then added to base solution. The solution is stirred for 3 hours, cooled and filtered. This then washed with hexane and dried.

The above tannate prepared reveals the following, with a yield of 45 gms:

Description: Yellowish, Tan, fine powder
Water: 3.92% w/w
Residue on ignition: 0.13% w/w
Heavy metals: Less than 5ppm
Tannic acid: 55.38% w/w
Chlorpheniramine base: 40.50% w/w
Assay: 99.80% w/w
Residual solvents: Isopropanol: 828 ppm

We claim:

1. The process for manufacturing pharmaceutical grade tannates, wherein
   a) Isopropanol is charged.
   b) Tannate base is added to this isopropanol.
   c) Tannic acid solution is prepared by dissolving in isopropanol.
   d) The above Tannic acid prepared is added into Tannate base solution.
   e) The solution as in (d) is stirred for a period of time at the said maximum temperature and then cooled.
   f) The material is centrifuged and washed with a volatile organic solvent.
   g) The material is then unloaded and dried.

2. The process, as claimed in claim 1 wherein the tannate base is selected from the group consisting of phenylephrine, carbetapentane, pyrilamine, chlorpheniramine, ephedrine, pseudoephedrine, brompheniramine, bromodiphenhydramine, diphenhydramine, pheniramine, Phenyltoxamine, clemastine, tripelennamine, cyproheptadine, phenindamine and phenyltoloxamine as a single ingredient or a combination of more than one.

3. The process, as claimed in claim 1 and 2 wherein the tannate base is Phenylephrine.

4. The process, as claimed in claim 1 and 2, wherein the tannate base is Chlorpheniramine.

5. The process as claimed in claim 1 wherein the step (e) is carried out for 3 hours.

6. The process as claimed in claim 6 wherein the process is carried out at temperature of 40-50°C.

7. The process as claimed in claim 1 wherein the volatile organic solvent used for washing in step (f) is hexane.

8. The process as claimed in claim 1 wherein the dried material contains isopropanol less than or equal to 0.5%.

9. The process as claimed in claim 1 and herein described in examples 1 to 2.